

INTRACYTOPLASMIC ULTRASTRUCTURES IN PERIPHERAL  
BLOOD CELLS IN LUPUS ERYTHEMATOSUS

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16. Abstract Buffy coats of peripheral blood of different manifestations of lupus erythematosus were studied by electron microscopy for the existence of the so-called viruslike intracytoplasmic tubular structures. They could always be demonstrated in the blood leukocytes of systemic lupus erythematosus independent of duration, severity and prior medical treatment of the disease, but were completely absent in chronic discoid lupus erythematosus. So far these inclusions have been observed only in the active dermal lesions of the chronic lupus erythematosus whereas various organs involved in systemic lupus erythematosus contained these structures. Their appearance in blood cells can therefore be interpreted as an early signal of visceral manifestation of the illness, which clinically is yet undetectable. Corresponding investigations in other systemic diseases as well as in healthy persons were negative.			
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INTRACYTOPLASMIC ULTRASTRUCTURES IN PERIPHERAL BLOOD CELLS IN  
LUPUS ERYTHEMATOSUS

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The detection of tubular or filamentary intracytoplasmic cell inclusions with a diameter of 200 - 350 Å<sup>0</sup>, which have been frequently termed 'virus-like' on the basis of their ultrastructural morphology, has been successful in various tissues in a large number of diseases up to now etiologically unrelated, especially in virus infections, neoplasms, diseases of the rheumatic type, the central nervous system, the kidneys, and the muscular system (tabulated survey by Kerl and Abock; Uzman). To our knowledge, these cytoplasmic inclusions have been identified in infiltrates or tumors of the skin in papulosis atrophicans maligna Degos [39], lymphomatoid papulosis [47], Kaposi sarcoma [19], mycosis fungoid and Sezary's Syndrome [46], and melanoma [6]. In Sjogren's Syndrome, they were identified in the kidneys [49] and parotid gland [30], and in diffuse scleroderma they were found in the skin [17, 30, 46] and in the kidneys [40]. While there has generally been only a single observation in most of the cases cited, in the case of dermatomyositis and especially with erythematosis, not only a large number of patients, but also various organs have been studied. In dermatomyositis, these tubular intracellular structures were found in the skin [9, 21, 22, 24, 25, 30, 31, 33, 41, 42, 46] and muscle [9, 24, 25, 30, 31, 41, 42].

In erythematosus integumentalis chronicus, they appear in fresh skin lesions [1, 4, 21, 22, 25, 27, 30, 44, 46, 48], but not in healthy skin or scarred and atrophied foci [1, 22, 25, 27, 44], on the other hand in visceral or systemic erythematosus they show up not only in clinically attacked areas [12, 22, 23, 26, 30, 34, 40, 44, 46, 48], but even in normal skin areas [12, 23, 30, 34, 38]. In the case of visceral erythematosus, moreover, the detection was successful in the kidneys [5, 7, 8, 11, 12, 14, 16, 20, 26, 28, 29, 35, 40, 43, 50-52], muscles [33, 40, 41], lungs [10], brain, heart, spleen [20], lymph nodes [20, 22, 27], and peripheral blood [2, 13, 15, 18, 36].

Since these structures have been found up to now in erythematosus integumentalis chronicus only in skin eruptions, the question is raised whether their occurrence in the cells of peripheral blood is an expression of a beginning, or an already spread of the disease to a systemic form.

We have therefore studied leukocyte concentrates of venous blood in the various symptomatic forms of erythematosus, with the electron microscope, for the appearance of this kind of intracytoplasmic inclusions.

#### Material and Methods

We analyzed the venous blood from 22 cases of erythematosus, some of whom have been under regular observation of the University Skin Clinic at Wurzburg for years, mostly from the beginning of the illness, and in whom the course of the disease up to this point is sufficiently well known. In this group are also three patients with a visceral erythematosus without skin involvement, who are in a sub-acute/acute stage of the disease. Studied besides them were six patients with other auto-immune diseases, mycosis fungoid, lymphogranulomatosis, leukemia, and one healthy

control case. Clinical data and the preceding therapy for all patients are given in the Tables.

Electron microscopic preparation. 10 ml of venous blood was mixed with 10 drops of Liquemin, and then centrifuged in small siliconized tubes at 1200 rpm. After carefully pipetting off the plasma, the remaining leucocyte layer (buffy coat) was carefully layered over with a 3% glutaraldehyde solution. After 20 minutes /37 of fixation, the leucocyte layer was detached from the glass with a pointed needle, taken out as a disc, and this was sliced into 1 mm wide strips. The single strips were then further fixed for 1.5 hours in 1% osmic acid, and after dehydration with increasing alcohol series, were imbedded in Epon. The slices prepared on the Ultramicrotome LKB I were treated for contrast development with uranyl acetate or uranyl acetate - lead citrate solution.

(Electron microscopic photography with the EM 9 A Zeiss).

All the material was generally thoroughly examined by two researchers for the intracytoplasmic virus-like structures in the blood cells.

### Results of the Study

#### A. Erythematosus integumentalis chronicus

The tubular intracytoplasmic structures occurring in skin lesions were not detectable in any of the ten cases of erythematosus integumentalis chronicus in cells of the peripheral blood. This group of patients did not offer either clinically nor immunohematologically any support for visceral manifestation up to this point. The duration of the disease amounted at the time of these studies from 1 to 25 years. In only one case was a Resochin treatment under way, and in all the others no internal therapy was followed in the last month before the study. In addition,

Table 1. Diagnosis, Clinical Data, and Study Results of the Patients.

Patient Number.	Age (yrs)	Duration of illness (yrs)	Diagnosis	Illness acuteness	Therapy (Internal)	Cytoplasmic inclusions		E-cells	Detection	
						Blood	Skin		Anti-nuclear factors	Anti-cytoplasmic factors
1 F	76	17	Integumental erythematosis	Chronic	∅	∅		∅		
2 F	36	11	Integumental erythematosis	Chronic	∅	∅		∅		∅
3 F	57	5	Integumental erythematosis	Chronic	∅	∅	+	∅		
4 F	15	3	Integumental erythematosis	Chronic	∅	∅		F		∅
5 M	43	8	Integumental erythematosis	Chronic	∅	∅		∅		∅
6 M	35	5	Integumental erythematosis	Chronic	∅	∅		∅		∅
7 M	34	1	Integumental erythematosis	Chronic	Resochin	∅		∅		∅
8 M	31	6	Integumental erythematosis	Chronic	∅	∅	+	∅		∅
9 M	40	10	Integumental erythematosis	Chronic	∅	∅		∅		
10 M	59	25	Integumental erythematosis	Chronic	∅	∅		∅		∅

Table 1. (cont).

11 M	67	1	Integumental erythematosis	Disseminated	Corticosteroid	+		∅		∅
12 M	45	8	Integumental erythematosis	Disseminated	∅	+	+	∅		∅
13 M	43	21	Integumental and visceral erythematosis	Chronic	∅	+		∅	∅	∅
14 M	34	3	Visceral erythematosis	Chronic	∅	+		+	+	
15 F	47	18	Visceral erythematosis	Chronic	Corticosteroid	+		+	+	
16 F	47	14	Visceral erythematosis	Chronic	Corticosteroid Methotrexate	+		+	+	
17 F	44	17	Integumental and visceral erythematosis	Chronic	Corticosteroid Imurek	+		+	+	
18 F	34	16	Integumental and visceral erythematosis	Chronic	Corticosteroid	+		+	+	
19 F	72	22	Integumental and visceral erythematosis	Chronic	Corticosteroid	+		∅	∅	+
20 F	27	1	Visceral erythematosis	Subacute	∅	+		+	+	
21 F	39	1 1/2	Visceral erythematosis	Subacute	Corticosteroid	+		+	+	
22 F	36	4	Visceral erythematosis	Subacute	Corticosteroid Imurek	+	∅	+	+	

Table 1. (cont).

Patient Number	Age (yrs)	Duration of illness (yrs)	Diagnosis	Illness acuteness	Therapy (Internal)	Cytoplasmic inclusions		E-cells	Detection	
						Blood	Skin		Anti- nuclear factors	Anti- cytoplasmic factors
23 F	40	4	Dermatomyositis		Corticosteroid Imurek	∅		∅		∅
24 F	46	12	Diffuse sclerodermia		∅	∅		∅		∅
25 F	48	28	Diffuse scleradermia		Metal- captase	∅		∅		∅
26 F	68	4	Sezary's Syndrome		∅	∅	∅			
27 F	17	1/2	Morbus Hodgkin		∅	∅				
28 M	57	1/4	Monocytic leukemia		Corticosteroid	∅				
29 F	32		Control			∅				

skin biopsies of typical hyperkeratotic discoid erythemic centers from two patients were studied and in these, the same results arose as in skin biopsies from erythematosus integumentalis disseminatus (see under B).

B. Erythematosus integumentalis chronicus with dissemination of skin involvement.

In two patients (No. 11 and 12), who showed a dissemination of skin involvement on the trunk and extremities at the time of the study, the characteristic intracytoplasmic structures were found in leucocytes of the peripheral blood. We could detect the same cytoplasmic inclusions in fibroblasts, histiocytes, lymphocytes, and macrophages of the cutaneous infiltrate, as well as in endothelial cells of the small vessels, and in the keratinocytes, but also extracellularly in a skin lesion excised from under the arm (case No. 12). In both patients, however, there occurred neither a clinically manifest participation of internal organs, nor could pathological, hematological, or immunoserological conditions be shown by repeated control tests. The duration of the disease to this point amounted to 1 or 8 years. The observation period in these cases is still relatively short.

C. Erythematosus visceralis (chronicus/subacutus) with and without skin involvement.

Ten patients with visceral erythematosus, half of whom showed skin phenomena, were studied. Several patients were in clinical remission and had been a long time without systemic treatment. /41  
One female patient was chosen during a deterioration of her condition, before introduction of therapy. The remaining patients were undergoing a systemic corticoid and/or immunosuppressive therapy. The visceral manifestations attacked the kidneys, the heart, the vessels, the serous membranes, and the joints. In all cases, a /42  
positive erythematosus cell phenomenon and/or corresponding

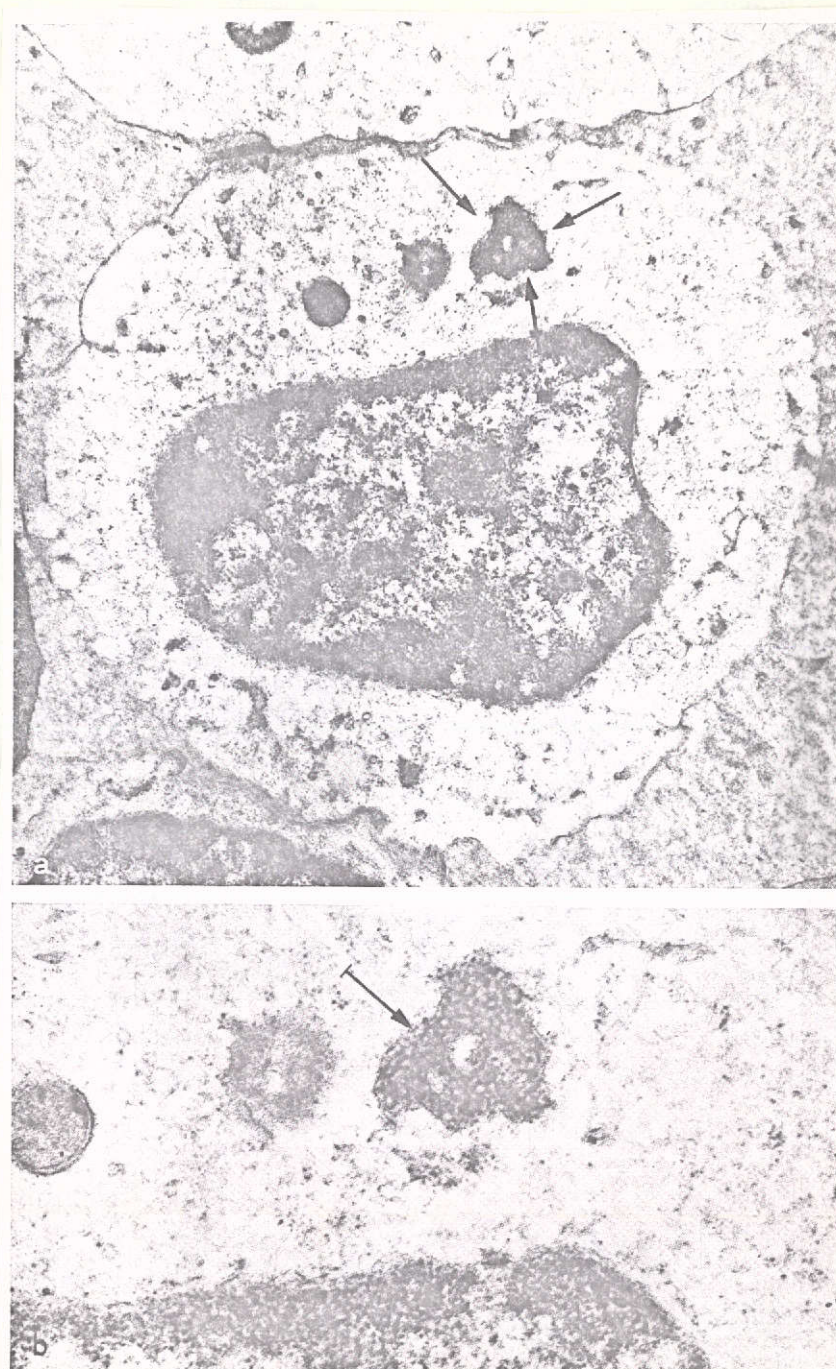


Figure 1. a. Patient No. 11 (Disseminated integumental erythematosus) In the cytoplasm, a clear blood leukosytic, electron-rich, tubular cell inclusion bound in a net-like form (arrow) at circumscribed location. Enlargement 15000:1; b. Section of 1. a. The unyielding membrane derived from the endoplasmic reticulum (arrow) not detectable in all sections. Enlargement 35000:1.

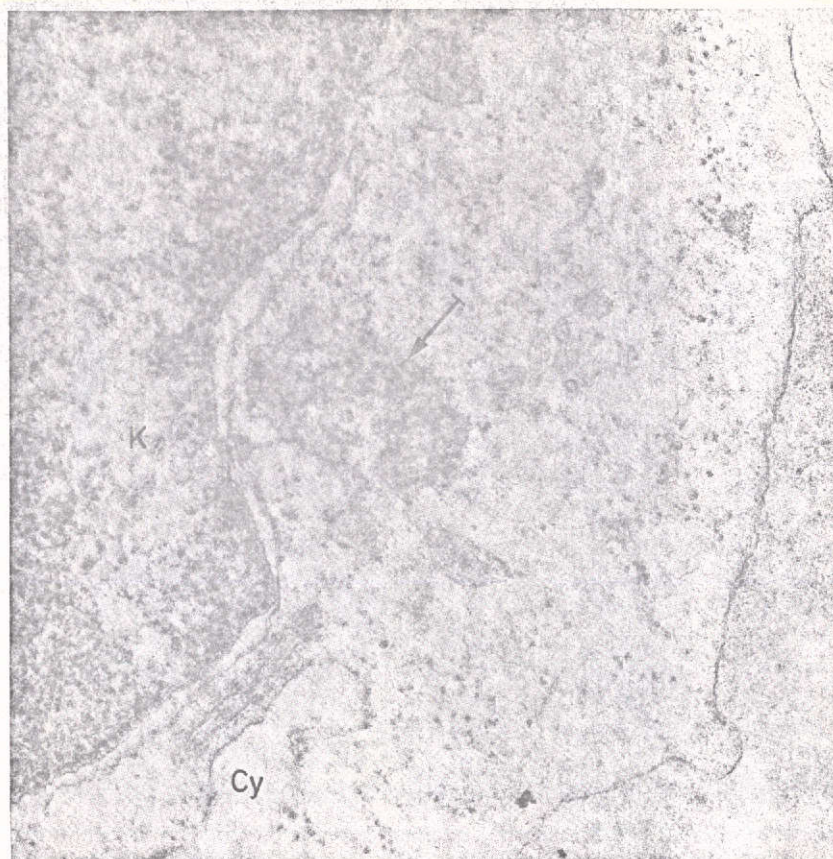


Figure 2. Patient No. 13 (Visceral erythematosis). Section of a blood lymphocyte. Tubular structures localized in the neighborhood of the nucleus (K), partly bound together by a membrane (arrow). Enlarged cisterns (C<sub>y</sub>) of the endoplasmic reticulum. Enlargement 45000:1.

immunological conditions (anti-nuclear/anti-cytoplasmic factors) were shown either before or by controls during this study, by means of indirect immunofluorescence or antiglobulin consumption test. The duration of illness of this group ranged from one to 22 years.

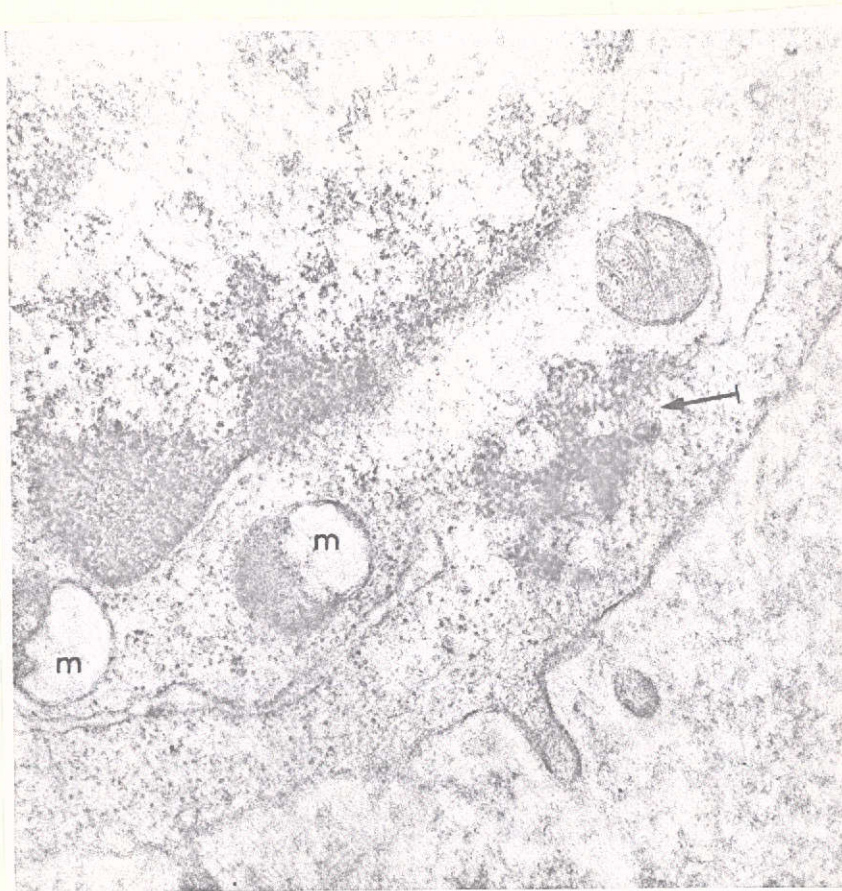


Figure 3. Patient No. 14 (Chronic visceral erythematosus). Bizarre configuration of accumulated tubular cell inclusions with indicated outer membrane (arrow) in the cytoplasm of a blood lymphocyte. Vacuolic degeneration of the mitochondria (m). Enlargement 40000:1.

In all cases, pathological tubular cell inclusions were found independently of the acuteness of the disease symptoms and pretreatment, in the cells of the leucocyte concentrates in variable abundance. In clinically unremarkable skin of a patient with progressive glomerulonephritis and severe heart involvement [No. 22], these structures were not detectable.

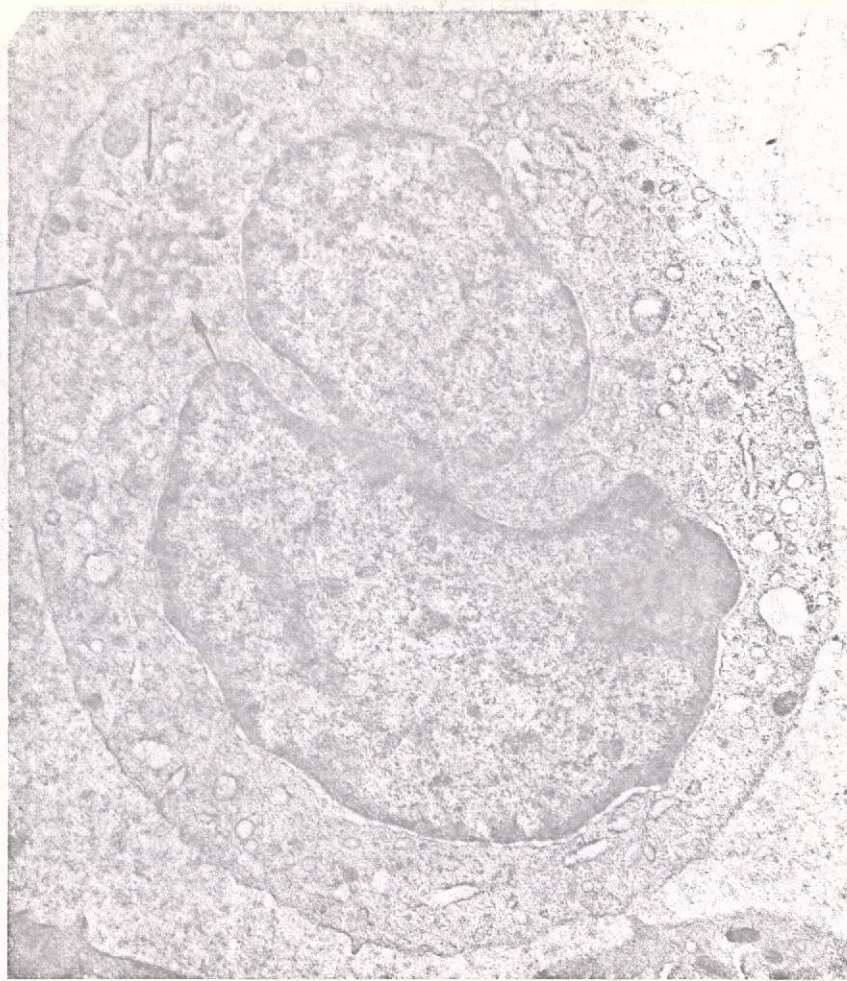


Figure 4. Patient No. 19 (Integumental and visceral erythematosis). Electron-rich, tubular, cytoplasmic inclusion within a granulocyte in the peripheral blood. Enlargement 15000:1.

#### D. Further systemic illnesses.

In patients with dermatomyositis, diffuse scleroderma, Sezary's Syndrome, Morbus Hodgkin, monocytic leukemia (No. 23-28), the study of the leucocyte concentrates turned out negative. Also, no corresponding tubular structures were found in the blood cells of the healthy control person.

#### E. Structure of the cell inclosures.

In leukocytes of the peripheral blood, the cell inclosures (especially with uranyl acetate contrasting),----- as electron-rich round -----

[TWO PAGES MISSING] [pp 44 and 45]

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[nulocten] --- of the peripheral blood in systemic erythematosus<sup>1./46</sup>. We ourselves could not detect these structures in blood cells in chronic discoid erythematosus. On the other hand, they were present in the studied cases of disseminated cutaneous erythematosus, and in all patients stricken with vsiceral erythematosus, in lymphocytes and lymphatic irritation forms. Granulocytes were attacked in two cases. A dependence on the severity of the clinical picture - acute disease attack or remission - and on the pre-treatment with corticosteroids and/or immunosuppressive drugs, could not be established. Studies on patients with dermatomyoositis, diffuse sclerodermis, Sezary's Syndrome, Morbus Hodgkin, and leukemia, as well as on one healthy control case, proved completely negative.

The localization of the tubular structures in the blood cells

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1. The work of J. H. Goodman et al [Ann. intern. Med 79, 396-402 (1973)] and P. M. Grimley et al [Arthr. and Rheum. 16, 313-323 (1973)] were available to us only after going to press.

We thank Miss G. Schenk for her painstaking technical assistance.

corresponds to that in the cells of other tissues. The anastomosed, net-like branched tubuli were found partly in enlarged cisterns of the endoplasmic reticulum, and partly free without the confining membrane. The inclusion-positive leucocytes show, as other authors have also observed [2, 24, 25, 38, 48], beginning degenerative changes (for example, enlarged and vacuolized mitochondria, augmented occurrence of lysosomes), which, however, are expressed differently from cell to cell. From the occurrence of the inclusions even in cells with completely unremarkable cytoplasmic structures, it was concluded that it could be a case here of an early indication of a cell injury [20].

The ultrastructural picture of the tubular cytoplasmic inclusions does not necessarily permit a conclusion about their etiology. On the basis of its detection in the most various human diseases, and experimental animal illness conditions, it is conjectured that it is a matter of a broad, unspecific, pathological phenomenon in the endoplasmic reticulum as an answer to various irritants [3, 8, 20, 42, 43]. However, they are discussed also as the morphological equivalent of a specific immunological mechanism [14, 30], and in combination with immunoglobulin production [53]. Their viral nature is not demonstrable from the electron microscopic structure and cannot, up to now, be ascertained either immunologically, serologically, nor by culturing (reviewed by Fischer and coworkers). Also, the description of intranuclear tubular or filamentary inclusions [23, 37, 48, 50], does not support this hypothesis, since this kind of structure could be taken completely for metabolic nuclear products [34]. In the specific study material, they were neither in 47 skin biopsies nor in leucocytes.

Although the occurrence of intracytoplasmic cell structures can not be considered as specific for erythematosus, their appearance in various organs in the visceral manifestation of the illness

seems to be characteristic. Thus, the series of electron microscopic studies of renal biopsy material revealed that tubular cytoplasmic inclusions in erythematous nephropathy could be detected in 62-100% [5, 12, 14, 28, 29, 52], preponderantly in the endothelial cells of the capillaries of the glomeruli. In a large number of other renal illnesses, on the other hand, they were found in about 2-4% [5, 14, 29, 52], and seldom in a higher percentage bracket of 20-26% [12, 28]. The observation seems important in this connection, that these structures in erythematous nephropathy appeared independently of the severity of the clinical picture and of the histologically expressed renal changes [12, 14, 20, 28, 35, 52]. Grausz and coworkers pursued the cases of two patients suffering from chronic integumental erythematosis, who showed cytoplasmic inclusions in renal endothelia with unlimited renal function and unremarkable histological renal condition. In both cases, a visceral erythematosis developed in the course of the observation time of 4 or 6 years. From this, it was concluded that these cytoplasmic structures might be an early diagnostic indication of a renal involvement in erythematosis [14, 52]. Also in the specific studies, no dependence of the appearance of the pathological cell structures in the blood on the duration and acuteness of the disease could be established in visceral erythematosis. They were detectable in cases of clinical remission lasting, in part, for years, at the same frequency as in new illnesses or in fresh attacks of the illness. Furthermore, they were found in two patients with disseminated integumental erythematosis with a tendency towards exacerbation. Although at this time the latter cannot be classified either clinically or immunoserologically as so-called transition forms, they seem to stand a strong risk of the development of visceral erythematosis.

Since even today classification of special forms of development in cutaneous or visceral erythematosis is still not possible,

in our opinion, the electron microscopic detection of these cytoplasmic inclusions in cells of peripheral blood - along with the study of serological immuno-phenomena - could prove to be important in the early diagnosis of a generalization of the disease.

### Literature

1. Auböck, L., Kerl, H.: Newer micromorphological aspects of Lupus erythematosus. Arch. Derm. Forsch. 244, 536-540 (1972).
2. Bariety, J., Amor, B., Kahan, A., Balafrej, J. L., Delbarre, F.: Ultrastructural anomalies in mononuclear cells of peripheral blood in S. L. E.: Presence of virus-like inclusions, Rev. Europ. Etud. Clin. Biol. 16, 715-720 (1971). /48
3. Baringer, J. R., Swoveland, P.: Tubular aggregates in endoplasmatic reticulum: evidence against their viral nature. J. Ultrastruct. Res. 41, 270-276 (1972).
4. Blank, H., Davis, C., Collins, C.: Electron microscopy for the diagnosis of cutaneous viral infections. Brit. J. Derm. 83, 69-80 (1970).
5. Bloodworth, J. M. B., Shelp, W. D.: Endothelial cytoplasmic inclusions. Arch. Path. 90, 252-258 (1970).
6. Cesarini, J. P., Prunieras, M.: Tubular inclusions of the Lupus type in malignant melanomas. Ann. Derm. Syph. (Paris) 99, 525 (1972).
7. Churg, J., Grishman, E.: Ultrastructure of immune deposits in renal glomeruli. Ann. intern. Med. 76, 479-486 (1972).
8. De Martino, C., Accini, L., Andres, G. A.: Tubular structures associated with the endothelial endoplasmic reticulum in glomerular capillaries of Rhesus monkey and nephritic man. Z. Zellforsch, 97, 502-511 (1969).
9. Feorino, P. M., Hierholzer, J. C., Norton, W. L.: Viral isolation studies of inclusion positive biopsy from human connective tissue diseases. Arthr. and Rheum. 13, 378-380 (1970).
10. Fraire, A. E., Smith, M. N., Greenberg, S. D., Weg, J. G., Sharp, J. T.: Tubular structures in pulmonary endothelial cells in systemic lupus erythematosus. Amer. J. clin. Path. 56, 244-248 (1971).
11. Fresco, R.: Virus-like particles in systemic lupus erythematosus. New Engl. J. Med. 283, 1231 (1970).
12. Garancis, J. C., Komorowski, R. A., Gerson, C. B., Straumfjord, J. V.: Significance of cytoplasmic microtubules in lupus nephritis. Amer. J. Path. 64, 1-8 (1971).

13. Georgieva, St.: Leucocyte destruction forms in acute lupus erythematoses. *Derm. i. Vener.* 10, 229-234 (1971).
14. Grausz, H., Early, L. E., Stephens, B. G., Lee, J. C., Hopper, J.: Diagnostic import of virus-like particles in the glomerular endothelium of patients with systemic lupus erythematosus. *New Engl. J. Med.* 283, 506-511 (1970).
15. Györkey, F., Györkey, P.: *Zit. n. Tisher*, C. C. Kelso, H. B., Robinson, R. R., Gunnels, J. C. Burkholder, P. M.: *Ann. intern. Med.* 75, 537 (1971).
16. Györkey, F., Min, K. W., Györkey, P.: Submicroscopic structures resembling myxovirus in 5 cases of hyman systemic lupus erythematosus (SLE). *Amer. J. Path.* 55, 13a (1969).
17. Györkey, F., Min, K. W., Györkey, P.: Myxovirus-like structures in human collagen diseases. *Arthr. and Rheum.* 12, 300 (1969).
18. Györkey, F., Sinkovics, J. G.: Microtubules of systemic lupus erythematosus. *Lancet* 1971 I, 131-132.
19. Györkey, F., Sinkovics, J. G., Györkey, P.: Electron microscopic observations on structures resembling myxovirus in human sarcomas. *Cancer* 27, 1449-1454 (1971).
20. Haas, J. E., Yunis, E. J.: Tubular inclusions of systemic lupus erythematosus. Ultrastructural observations regarding their possible viral nature. *Exp. molec. Path.* 12, 257-263 (1970).
21. Hashimoto, K.: Paramyxovirus-like structures in lupus and dermatomyositis. *Proc. Electr. micr. Soc. Amer.*, p. 222-223 (1969).
22. Hashimoto, K.: Parmyxovirus-like inclusions in several skin diseases of unknown etiology. *Clin. Res.* 18, 349 (1970).
23. Hashimoto, K., Chandler, R. W.: Paramyxovirus-like inclusions /49 in systemic lupus erythematosus. *Acta. dermat.-venereol. (Stockh.)* 52, 263-277 (1972).
24. Hashimoto, K., Robison, L., Velayos, E., Niizuma, K.: Dermatomyositis. Electron microscopic immunologic and tissue culture studies of paramyxovirus-like inclusions. *Arch. Derm.* 103, 120-135 (1971).
25. Hashimoto, K., Thompson, D. F.: Discoid lupus erythematosus. Electron microscopic studies of paramyxovirus-like structures. *Arch. Derm.* 101, 565-577 (1970).
26. Haustein, U. F.: Elektron microscopic studies of the virogenesis of Lupus erythematosus. *Derm. Mschr.* 158, 485-491 (1972).
27. Haustein, U. F.: Unusual nuclear inclusion in leukocytes and basal cells of the skin in Lupus erythematosus. *Dermatologica (Basel)* 146, 132-137 (1973).
28. Hurd, E. R., Eigenbrodt, E., Ziff, M., Strunk, S. W.: Cytoplasmic tubular structures in kidney biopsies in systemic lupus erythematosus. *Arthr. and Rheum.* 12, 541-542 (1969).

29. Kawano, K., Miller, L., Kimmelstiel, P.: Virus-like structures in lupus erythematosus, *New Engl. J. Med.* 281, 1228-1229 (1969).
30. Kerl, H., Auböck, L.: Virus-like endoplasmic structures in Lupus erythematosus and in various other etiologically unclear illnesses. *Hautarzt* 24, 95-105 (1973).
31. Kiraly, K., Horvath, A. Daroczy, J., Nagy, E.: Immunological aspects of dermatomyositis. *Allergie Immunol.* 18, 141-160 (1962).
32. Klug, H., Sönnischen, N.: Electron microscopic studies of the detection of virus-like particles in dermatomyositis. *Derm. Mschr.* 159, 97-102 (1973).
33. Klug, H. Sönnichsen, N.: Electron microscopic studies of muscle in Lupus erythematosus. *Derm. Mschr.* 159, 577-593 (1973).
34. Kobayasi, T., Asboe-Hansen, G.: Virus particles in Lupus erythematosus. *Acta dermat.-venereol. (Stockh.)* 52, 425-434 (1972).
35. Laugier, P., Orusco, M., Chatelanat, F., Humair, L., Posternak, F.: Disseminated Lupus erythematosus induced by estrogens. Viral inclusions revealed in renal biopsy. *Bull Soc. franc. Derm. Syph.* 78, 623-628 (1971).
36. Müller-Hermelink, H. K., Lennert, K.: Virus-like structures in a lymph node in visceral Lupus erythematosus. *Virchows Arch., Abt. B. Zellpath.* 7, 367-370 (1971).
37. Müller-Hermelink, H. K., Lennert, K.: Virus-like structures in leucocytes of the peripheral blood in visceral Lupus erythematosus. *Klin. Wschr.* 49, 661-663 (1971).
38. Nieland, N. W., Hashimoto, K., Masi, A. T.: Microtubular inclusions in normal skin of systemic Lupus erythematosus patients. *Arthr. and Rheum.* 15, 193-200 (1972).
39. Nishida, S., Howard, R. O.: Is Degos disease of viral origin? *Lancet* 1968 I, 1200.
40. Norton, W. L.: Endothelial inclusions in active lesions of systemic Lupus erythematosus. *J. Lab. clin. Med.* 74, 369-379 (1969).
41. Norton, W. L.: Comparison of the microangiopathy of systemic Lupus erythematosus, dermatomyositis, scleroderma and diabetes mellitus. *Lab. Invest* 22, 301-308 (1970).
42. Norton, W. L., Velayos, E., Robison, L.: Endothelial inclusions in dermatomyositis. *Ann. rheum. Dis.* 29, 67-72 (1970).
43. Pincus, T., Blacklow, N. R., Grimley, P. M., Bellanti, J. A.: Glomerular microtubules of systemic Lupus erythematosus. *Lancet* 1970 II, 1058-1061.
44. Prunieras, M., Grupper, C.: Initial attempt at correlation of clinical, serological, microscopic, optical, and electronic studies of 42 cases of Lupus erythematosus. *Bull. Soc. franc. Derm. Syph.* 77, 843-847 (1970).

45. Prunieras, M., Grupper, C., Durepaire, R., Beltzer-Gareilly, E., Regnier, M.: Ultrastructural study of the skin in 42 cases of Lupus erythematosus. *Presse med.* 78, 2475-2479 (1970).
46. Prunieras, M., Grupper, C., Durepaire, R., Eisenmann, D., Regnier, M.: The inclusions of the Lupus type in the skin. *Nouv. Presse med.* 1, 1133-1138 (1972).
47. Sandbank, M., Feuerman, E. J.: Lymphomatoid papulosis. *Acta dermat.-venereol.* (Stockh.) 52, 337-345 (1972).
48. Schmitt, D., Thivolet, J., Perrot, H., Leung Tack, J., Germain, D.: Ultrastructural aspects of the viral type in cutaneous lesions of acute Lupus and of fixed discoid Lupus. *Arch. Derm. Forsch.* 241, 317-328 (1971).
49. Shearn, M. A., Tu, W. H., Stephens, B. G.: Virus-like structures in Sjögren's syndrome. *Lancet* 1970 I, 568-569.
50. Sinkovics, J. G., Györkey, F., Thoma, G. W.: A rapidly fatal case of systemic Lupus erythematosus: Structures resembling viral nucleoprotein strands in the kidney and activities of lymphocytes in culture. *Tex. Rep. Biol. Med.* 27, 887-908 (1969).
51. Tannenbaum, M., Hsu, K. C., Buda, J., Grant, P., Lattes, C., Lattimer, J. K.: Electron microscopic virus-like material in systemic Lupus erythematosus: with preliminary immunologic observations on presence of measles antigen. *J. Uroi.* (Baltimore) 105, 615-619 (1971).
52. Tischer, C. C., Kelso, H. B., Robinson, R. R., Gunnells, J. C., Burkholder, P. M.: Intraendothelial inclusions in kidneys of patients with systemic lupus erythematosus. *Ann. intern. Med.* 75, 537-547 (1971).
53. Uzman, B. G., Saito, H., Kasac, M.: Tubular arrays in the endoplasmic reticulum in human tumor cells. *Lab. Invest.* 24, 492-498 (1971).

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